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(21) International Application Number: PCT/CA99/00541 (22) International Filing Date: 10 June 1999 (10.06.99) (30) Priority Data: 2,241,342 15 June 1998 (15.06.98) CA (71)(72) Applicant and Inventor: SHERMAN, Bernard, Charles [CA/CA]; 50 Old Colony Road, Willowdale, Ontario M2L 2K1 (CA).		(81) Designated States: AU, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN (57) Abstract A pharmaceutical tablet which incorporates two smaller tablets, one of which comprises an NSAID and the other of which comprises misoprostol.		

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PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

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BACKGROUND OF THE INVENTION

The invention herein is directed to a pharmaceutical tablet which comprises both an NSAID and misoprostol.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a class of drugs which have long been recognized as having high therapeutic value especially for the treatment of inflammatory conditions such as exhibited in inflammatory diseases like osteoarthritis and rheumatoid arthritis. While the NSAIDs present a beneficial therapeutic value, they also exhibit undesirable side effects. An especially undesirable side effect of the administration of NSAIDs is the ulcerogenic effects generally associated with chronic use. NSAID induced ulcers in the stomach can be dangerous. Such ulcers generally exhibit few or no symptoms and may cause dangerous bleeding when undetected. In some instances, bleeding ulcers can prove fatal.

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Certain prostaglandins have been shown to prevent NSAID induced ulcers. Misoprostol is a prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers in many countries, including the United States.

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It is desirable to provide a pharmaceutical composition which exhibits the beneficial properties of an NSAID and which also exhibits the beneficial properties of misoprostol for countering the ulcerogenic side effects attendant to NSAID administration.

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This can be achieved by combining an NSAID and misoprostol in a single pharmaceutical tablet. However this is not easy to do, because misoprostol is highly unstable, and it is thus desirable not to have the misoprostol and NSAID mixed together, so as to prevent any deleterious effect of the NSAID on the stability of the misoprostol.

One solution to this problem, which is disclosed in US Patent 5601843, is to produce a tablet consisting of an inner core which comprises the NSAID and a mantle which surrounds the inner core and comprises the misoprostol. It is also disclosed that, in order to prevent contact between the misoprostol and the NSAID at the surface of the inner core, the inner core may be coated with an inert coating. Such coating may be an enteric coating, which also serves to reduce the likelihood of the NSAID dissolving in the stomach and thereby prevent exposing the stomach to the NSAID.

While the invention of US Patent 5601843 accomplishes its objective of separating the NSAID from the misoprostol, it has certain disadvantages. One disadvantage is the need to have a coating on the inner core in order to completely prevent contact between the NSAID in the inner core and the misoprostol in the mantle.

A second disadvantage is that the misoprostol is dispersed throughout the mantle, and is thus exposed to the environment at the surface of the tablet. This exposure increases the vulnerability of the misoprostol to degradation due to the effects of light or atmospheric oxygen and moisture.

The object of the present invention is to enable a pharmaceutical tablet that incorporates both an NSAID and misoprostol, but overcomes these disadvantages.

BRIEF SUMMARY OF THE INVENTION

5 The present invention is a pharmaceutical composition in the form of a tablet in which two smaller tablets are embedded, one of which comprises an NSAID and the second of which comprises misoprostol.

DETAILED DESCRIPTION OF THE INVENTION

10 Pharmaceutical tablets are routinely made on a tablet press. In the tableting process, a mixture of materials in the form of a free flowing powder or granular mix is filled into a metal die, into which a metal punch protrudes from beneath. A second metal punch is then inserted into the die from above, and pressure is applied to the upper and lower punches to cause the powder or
15 granular mix to be compressed into a tablet. The upper punch is then withdrawn, and the tablet is ejected from the die by raising the lower punch further into the die.

20 Compositions (i.e. tablets) of the present invention may be made as follows:

1. Firstly, a tablet comprising the NSAID and a tablet comprising the misoprostol are made in separate tableting operations. The portion of the composition which surrounds the two smaller tablets will be referred to herein as the "shell".
25
2. Then the final composition is assembled in a further tableting operation as follows:
 - (i) Part of the powder or granular mix of which the shell is to be
30 comprised is filled into the die, into which a punch has been inserted from below.

- 5
- (ii) One of the smaller tablets comprising the NSAID and one of the smaller tablets comprising the misoprostol are then inserted into the die.
- (iii) The balance of the powder or granular mix of which the shell is to be comprised is then filled into the die to cover two smaller tablets.
- 10
- (iv) The upper punch is then inserted into the die from above and pressure is applied between the punches to compress the powder or granular mix around the two smaller tablets into the form of the final tablet.
- 15
- (v) The upper punch is then withdrawn and the lower punch is raised further into the die to eject the composition.

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The NSAID contained within one of two smaller tablets will preferably be piroxicam or diclofenac or a salt of diclofenac such as diclofenac sodium or diclofenac potassium. Most preferably, the NSAID will be diclofenac sodium.

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Where diclofenac or a salt thereof is used, the amount per tablet will preferably be from 25 to 75 mg. The tablet containing diclofenac or salt thereof will contain, along with the diclofenac or salt thereof, usual tablet excipients such as binders, lubricants, fillers and the like. Preferably, the tablet containing the diclofenac or salt thereof will be coated with an enteric film coating to prevent the diclofenac or salt thereof from dissolving until after it has passed through the stomach and entered the small intestine. The enteric coating can be formulated with any suitable enteric coating polymer,

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many of which are known to those skilled in the art.

Where piroxicam is used as the NSAID, the amount per tablet will preferably be 10 to 20 mg. Again the tablet containing piroxicam will also comprise usual tablet excipients.

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The tablet containing the misoprostol will also include, along with the misoprostol, usual tableting excipients. The misoprostol will preferably be used in the form of a dispersion in hydroxypropyl methylcellulose, which is known in the prior art to improve the stability of misoprostol. The quantity of misoprostol per tablet will preferably be about 200 µg.

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The shell which surrounds the tablet containing the NSAID and the tablet containing the misoprostol will be comprised of usual tablet excipients, without any active medicinal ingredient mixed therein.

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The invention will be further understood from the following example, which is intended to be illustrative and not limiting of the scope of the invention.

EXAMPLE 1

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Tablets containing diclofenac sodium are made with a composition as follows:

	<u>Amount per tablet</u>
Diclofenac sodium	50.0 mg
Microcrystalline cellulose	24.0 mg
Magnesium stearate	1.0 mg
Croscarmellose sodium	<u>5.0 mg</u>
	80.0 mg

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These cores are then optionally enteric coated by spraying onto them a suspension or solution of an enteric coating polymer and a plasticizer.

EXAMPLE 2

Tablets containing misoprostol are made with a composition as follows:

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	<u>Amount per tablet</u>
Misoprostol 1% dispersion in	
hydroxypropyl methylcellulose	20.0 mg
Microcrystalline cellulose	8.5 mg
10 Magnesium stearate	0.5 mg
Croscarmellose sodium	<u>1.0 mg</u>
	30.0 mg

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EXAMPLE 3

A powder mix for producing the shell of the final tablet is prepared as a mixture of 99.5% by weight microcrystalline cellulose and 0.5% magnesium stearate.

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EXAMPLE 4

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The final composition is then made by making tablets from the mix of Example 3 and embedding in each such tablet one tablet from Example 1 and one tablet from Example 2, by the procedure previously described; that is to say, using a tablet press equipped to insert one tablet from Example 1 and one tablet from Example 2 as well as a quantity of the powder mix for the shell from Example 3 into a die, and making the final tablet by compression between a lower punch and an upper punch inserted into the die from below and above respectively.

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CLAIMS:

- 5 1. A pharmaceutical tablet in which are imbedded two smaller tablets, one
 of which comprises an NSAID and the other of which comprises
 misoprostol.
2. A pharmaceutical tablet as is Claim 1 wherein the NSAID is piroxicam.
- 10 3. A pharmaceutical tablet as in Claim 1 wherein the NSAID is selected
 from diclofenac and salts thereof.
4. A pharmaceutical tablet as in Claim 2, wherein the amount of piroxicam
 is from about 10 mg to about 20 mg.
- 15 5. A pharmaceutical tablet as in Claim 3, wherein the amount of
 diclofenac or a salt thereof is from about 25 mg to about 75 mg.
6. A pharmaceutical tablet as in any of Claims 1 to 5, wherein the amount
20 of misoprostol is about 200 µg.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/557 A61K31/54 A61K9/20 A61K9/28
 //(A61K31/557,31:54,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X, Y	EP 0 864 324 A (BASF AG) 16 September 1998 (1998-09-16) the whole document ---	1-6
X, Y	DE 196 37 479 A (BASF AG) 19 March 1998 (1998-03-19) the whole document ---	1-6
X, Y	WO 98 10752 A (BREITENBACH JOERG ; BASF AG (DE); KLEINKE ANDREAS (DE); ROSENBERG J) 19 March 1998 (1998-03-19) the whole document ---	1-6
X, Y	US 5 601 843 A (GIMET RENE A ET AL) 11 February 1997 (1997-02-11) cited in the application the whole document --- -/--	1-6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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PCT/CA 99/00541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 91 16886 A (SEARLE & CO) 14 November 1991 (1991-11-14) the whole document ---	1-6
X,Y	WO 91 16895 A (SEARLE & CO) 14 November 1991 (1991-11-14) the whole document ---	1-6
Y	WO 95 34291 A (DUMEX LTD AS ;NORLING TOMAS (DK); JENSEN LONE NOERGAARD (DK); HANS) 21 December 1995 (1995-12-21) the whole document ---	1-6
Y	WO 98 18610 A (LENGERICH BERNHARD H VAN) 7 May 1998 (1998-05-07) figure 4 ---	1
A	EP 0 465 234 A (MCNEIL PPC INC) 8 January 1992 (1992-01-08) ---	
A	US 5 015 481 A (FRANZ MICHEL ET AL) 14 May 1991 (1991-05-14) ---	
A	WO 97 15319 A (UNIV KINGSTON ;ANASTASSIADES TASSOS (CA)) 1 May 1997 (1997-05-01) ---	
A	US 5 232 704 A (FRANZ MICHEL R ET AL) 3 August 1993 (1993-08-03) ---	
A	DE 196 02 757 A (BOEHRINGER MANNHEIM GMBH) 31 July 1997 (1997-07-31) -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intr. National Application No

PCT/CA 99/00541

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0864324 A	16-09-1998	DE 19710213 A CA 2229614 A CN 1196929 A JP 10314279 A	17-09-1998 12-09-1998 28-10-1998 02-12-1998
DE 19637479 A	19-03-1998	AU 4384697 A CZ 9900829 A WO 9810752 A EP 0930875 A HR 970485 A	02-04-1998 16-06-1999 19-03-1998 28-07-1999 31-08-1998
WO 9810752 A	19-03-1998	DE 19637479 A DE 19734011 A AU 4384697 A CZ 9900829 A EP 0930875 A HR 970485 A	19-03-1998 11-02-1999 02-04-1998 16-06-1999 28-07-1999 31-08-1998
US 5601843 A	11-02-1997	US 5698225 A AT 121625 T AU 7876491 A CA 2082944 A,C DE 69109286 D DE 69109286 T DK 527887 T EP 0527887 A ES 2071312 T GR 3015939 T IE 68596 B IL 98033 A PT 97562 A,B WO 9116895 A	16-12-1997 15-05-1995 27-11-1991 04-11-1991 01-06-1995 28-09-1995 03-07-1995 24-02-1993 16-06-1995 31-07-1995 26-06-1996 31-07-1995 28-02-1992 14-11-1991
WO 9116886 A	14-11-1991	AU 8089091 A IE 62050 B IL 98034 A PT 97550 A,B US 5213807 A	27-11-1991 14-12-1994 31-10-1996 28-02-1992 25-05-1993
WO 9116895 A	14-11-1991	AT 121625 T AU 7876491 A CA 2082944 A,C DE 69109286 D DE 69109286 T DK 527887 T EP 0527887 A ES 2071312 T GR 3015939 T IE 68596 B IL 98033 A PT 97562 A,B US 5601843 A US 5698225 A	15-05-1995 27-11-1991 04-11-1991 01-06-1995 28-09-1995 03-07-1995 24-02-1993 16-06-1995 31-07-1995 26-06-1996 31-07-1995 28-02-1992 11-02-1997 16-12-1997
WO 9534291 A	21-12-1995	AT 177944 T AU 697456 B AU 2732795 A CA 2192086 A	15-04-1999 08-10-1998 05-01-1996 21-12-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00541

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9534291 A		DE 69508580 D EP 0765157 A ES 2131318 T FI 965003 A NO 965381 A NZ 288185 A	29-04-1999 02-04-1997 16-07-1999 13-12-1996 13-02-1997 26-02-1998
WO 9818610 A	07-05-1998	AU 4991597 A EP 0935523 A NO 992036 A	22-05-1998 18-08-1999 28-04-1999
EP 0465234 A	08-01-1992	AU 656140 B AU 8014091 A CA 2046079 A JP 4230329 A	27-01-1995 09-01-1992 04-01-1992 19-08-1992
US 5015481 A	14-05-1991	NONE	
WO 9715319 A	01-05-1997	AU 7271996 A	15-05-1997
US 5232704 A	03-08-1993	NONE	
DE 19602757 A	31-07-1997	AU 1594897 A BR 9707083 A CA 2243964 A CN 1214629 A CZ 9802320 A WO 9726867 A EP 0877605 A NO 983437 A PL 328157 A ZA 9700596 A	20-08-1997 23-03-1999 31-07-1997 21-04-1999 14-10-1998 31-07-1997 18-11-1998 28-09-1998 18-01-1999 24-07-1998